

SECTION 2: SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

Meropenem

500 mg & 1 g Powder for Solution for IV Injection or Infusion

Meropenem (as Meropenem Trihydrate)

1. NAME OF THE MEDICINAL PRODUCT

Meropenem Powder for Solution for IV Injection or Infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Meropenem 500 mg Powder for Solution for IV Injection or Infusion

Each vial contains meropenem trihydrate equivalent to 500 mg anhydrous meropenem.

Meropenem 1 g Powder for Solution for IV Injection or Infusion

Each vial contains meropenem trihydrate equivalent to 1 g anhydrous meropenem.

Excipients:

Each 500 mg vial contains 104 mg sodium carbonate which equates to approximately 2.0 mEq of sodium (approximately 45 mg).

Each 1 g vial contains 208 mg sodium carbonate which equates to approximately 4.0 mEq of sodium (approximately 90 mg).

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for IV injection or infusion.

Meropenem is a white to light yellow powder.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Meropenem is indicated for the treatment of the following infections in adults and children over 3 months of age:

- Severe pneumonia, including hospital and ventilator-associated pneumonia.
- Broncho-pulmonary infections in cystic fibrosis
- Complicated urinary tract infections
- Complicated intra-abdominal infections

- Complicated gynecologic infections, intra- and post-partum infections
- Complicated skin and soft tissue infections
- Acute bacterial meningitis
- Treatment of patients with bacteremia that occurs in association with, or is suspected to be associated with, any of the infections listed above.

Meropenem may be used in the management of neutropenic patients with fever that is suspected to be due to a bacterial infection.

Consideration should be given to official guidelines on the appropriate use of antibacterial agents.

4.2. Posology and method of administration

The tables below provide general recommendations for dosing.

The dose of meropenem administered and the duration of treatment should take into account the type of infection to be treated, including its severity, and the clinical response.

A dose of up to 2 g three times daily in adults and adolescents and a dose of up to 40 mg/kg three times daily in children may be particularly appropriate when treating some types of infections, such as infections due to less susceptible bacterial species (e.g. *Enterobacteriaceae*, *Pseudomonas aeruginosa*, *Acinetobacter* spp.), or very severe infections.

Adults and adolescents with normal renal function (creatinine clearance (CrCl) greater than 51 ml/min)

Site and Type of Infection	Dose to be administered every 8 hours
Severe pneumonia including hospital and ventilator-associated pneumonia.	500 mg or 1 g
Broncho-pulmonary infections in cystic fibrosis	2 g
Complicated urinary tract infections	500 mg or 1 g
Complicated intra-abdominal infections	500 mg or 1 g
Intra- and post-partum infections	500 mg or 1 g
Complicated skin and soft tissue infections	500 mg or 1 g
Acute bacterial meningitis	2 g
Management of febrile neutropenic patients	1 g

Adults and adolescents with renal impairment. The dose for adults and adolescents should be adjusted when creatinine clearance is less than or equal to 50 ml/min, as shown below. There are limited data to support the application of these dose adjustments for a unit dose of 2 g.

Creatinine Clearance	Dose (based on “unit” dose range of 500 mg or 1 g or 2 g, see table above)	Frequency
26-50	one unit dose	every 12 hours
10-25	half of one unit dose	every 12 hours
<10	half of one unit dose	every 24 hours

Meropenem is cleared by hemodialysis and hemofiltration. The required dose should be administered after completion of the hemodialysis cycle.

There are no established dose recommendations for patients receiving peritoneal dialysis.

Hepatic impairment. No dose adjustment is necessary in patients with hepatic impairment (see section 4.4).

Dose in elderly patients. No dose adjustment is required for the elderly with normal renal function or creatinine clearance values above 50 ml/min.

Pediatric population. Children under 3 months of age

The safety and efficacy of meropenem in children under 3 months of age have not been established and the optimal dose regimen has not been identified. However, limited pharmacokinetic data suggest that 20 mg/kg every 8 hours may be an appropriate regimen.

Children from 3 months to 11 years of age and up to 50 kg body weight with normal renal function

The recommended dose regimens are shown in the table below:

Site and Type of Infection	Dose to be administered every 8 hours
Severe pneumonia including hospital and ventilator-associated pneumonia	10 or 20 mg/kg
Broncho-pulmonary infections in cystic fibrosis	40 mg/kg
Complicated urinary tract infections	10 or 20 mg/kg
Complicated intra-abdominal infections	10 or 20 mg/kg
Complicated skin and soft tissue infections	10 or 20 mg/kg
Acute bacterial meningitis	40 mg/kg
Management of febrile neutropenic patients	20 mg/kg
Severe pneumonia including hospital and ventilator-associated pneumonia	10 or 20 mg/kg

Children over 50 kg body weight

The adult dose should be administered.

There is no experience in children with renal impairment.

Method of administration

Meropenem is usually given by intravenous infusion over approximately 15 to 30 minutes. Alternatively, meropenem doses of up to 20 mg/kg may be given as an intravenous bolus over approximately 5 minutes. There are limited safety data available to support the administration of a 40 mg/kg dose in children as an intravenous bolus injection.

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

4.3. Contraindications

Hypersensitivity to meropenem or to any of the excipients listed in section 6.1.

Hypersensitivity to any other carbapenem antibacterial agent.

Severe hypersensitivity (e.g. anaphylactic reaction, severe skin reaction) to any other type of beta-lactam antibacterial agent (e.g. penicillins or cephalosporins).

4.4. Special warnings and precautions for use

Hypersensitivity reactions

As with all beta-lactam antibiotics, serious and occasionally fatal hypersensitivity reactions have been reported (see sections 4.3 and 4.8).

Patients who have a history of hypersensitivity to carbapenems, penicillins or other beta-lactam antibiotics may also be hypersensitive to meropenem. Before initiating therapy with meropenem, careful inquiry should be made concerning previous hypersensitivity reactions to beta-lactam antibiotics.

If a severe allergic reaction occurs, the medicinal product should be discontinued and appropriate measures taken.

Antibiotic-associated colitis

Antibiotic-associated colitis and pseudomembranous colitis have been reported with nearly all anti-bacterial agents, including meropenem, and may range in severity from mild to life threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea during or subsequent to the administration of meropenem (see section 4.8).

Discontinuation of therapy with meropenem and the administration of specific treatment for *Clostridium difficile* should be considered. Medicinal products that inhibit peristalsis should not be given.

Seizures

Seizures have infrequently been reported during treatment with carbapenems, including meropenem (see section 4.8).

Hepatic function monitoring

Patients with pre-existing liver disorders should have liver function monitoring during treatment with meropenem. There is no dose adjustment necessary.

Direct antiglobulin test (Coombs test) seroconversion

A positive direct or indirect Coombs test may develop during treatment with meropenem.

Concomitant use with valproic acid/sodium valproate/valpromide

The concomitant use of meropenem and valproic acid/sodium valproate/valpromide is not recommended (see section 4.5).

Pediatric population

Meropenem is licensed for children over 3 months of age. There is no evidence of an increased risk of any adverse drug reaction in children based on the limited available data. All reports received were consistent with events observed in the adult population.

Enterobacteriaceae, Pseudomonas aeruginosa and Acinetobacter spp. resistance

Resistance to penems of *Enterobacteriaceae*, *Pseudomonas aeruginosa*, *Acinetobacter* spp. varies across the countries. Prescribers are advised to take into account the local prevalence of resistance in these bacteria to penems.

Meropenem contains sodium.

Meropenem contains sodium.

Meropenem 500 mg: This medicinal product contains approximately 2.0 mEq of sodium per 500 mg dose which should be taken into consideration by patients on a controlled sodium diet.

Meropenem 1.0 g: This medicinal product contains approximately 4.0 mEq of sodium per 1.0 g dose which should be taken into consideration by patients on a controlled sodium diet.

4.5. Interaction with other medicinal products and other forms of interaction

No specific medicinal product interaction studies other than probenecid were conducted. Probenecid competes with meropenem for active tubular secretion and thus inhibits the renal excretion of meropenem with the effect of increasing the elimination half-life and plasma concentration of meropenem. Caution is required if probenecid is co-administered with meropenem.

The potential effect of meropenem on the protein binding of other medicinal products or metabolism has not been studied. However, the protein binding is so low that no interactions with other compounds would be expected on the basis of this mechanism.

Decreases in blood levels of valproic acid have been reported when it is co-administered with carbapenem agents resulting in a 60-100 % decrease in valproic acid levels in about two days. Due to the rapid onset and the extent of the decrease, co-administration of valproic acid/sodium valproate/valpromide with carbapenem agents is not considered to be manageable and therefore should be avoided.

Oral anti-coagulants

Simultaneous administration of antibiotics with warfarin may augment its anti-coagulant effects. There have been many reports of increases in the anti-coagulant effects of orally administered anti-coagulant agents, including warfarin in patients who are concomitantly receiving antibacterial agents. The risk may vary with the underlying infection, age and general status of the patient so that the contribution of the antibiotic to the increase in INR (international normalised ratio) is difficult to assess. It is recommended that the INR should be monitored frequently during and shortly after co-administration of antibiotics with an oral anti-coagulant agent.

4.6. Fertility, pregnancy and lactation

Pregnancy. There are no or limited amount of data from the use of meropenem in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. As a precautionary measure, it is preferable to avoid the use of meropenem during pregnancy.

Breast-feeding. It is unknown whether meropenem is excreted in human milk. Meropenem is detectable at very low concentrations in animal breast milk. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from meropenem therapy taking into account the benefit of therapy for the woman

4.7. Effects on ability to drive and use machines

No studies on the effect on the ability to drive and use machines have been performed. However, when driving or operating machines, it should be taken into account that headache, parasthesia and convulsions have been reported for meropenem.

4.8. Undesirable effects

a. Summary of the safety profile

Meropenem is tolerated well when it is used in recommended dosages and dosing regimens. In a review of 4 872 patients with 5 026 meropenem treatment exposures, meropenem-related adverse reactions most frequently reported were diarrhea (2.3 %), rash (1.4 %), nausea/vomiting (1.4 %) and injection site inflammation (1.1 %). The most commonly reported meropenem-related laboratory adverse events were thrombocytosis (1.6 %) and increased hepatic enzymes (1.5-4.3 %).

b. Tabulated list of adverse reactions

For estimation of development frequency of side effects the following criteria are used: very common ($\geq 1/10$), common (from $\geq 1/100$ to $< 1/10$), uncommon (from $\geq 1/1000$ to $< 1/100$), rare (from $\geq 1/10\ 000$ to $< 1/1000$), very rare (from $< 1/10\ 000$ including individual case safety report), and “the frequency is not known” (according to the available data, it is not possible to estimate the frequency).

System Organ Class	Frequency	Event
<i>Infections and infestations</i>	Uncommon	oral and vaginal candidiasis
<i>Blood and lymphatic system disorders</i>	Common	thrombocythemia
	Uncommon	eosinophilia, thrombocytopenia, leucopenia, neutropenia, agranulocytosis, hemolytic anemia
<i>Immune system disorders</i>	Uncommon	angioedema, anaphylaxis
<i>Nervous system disorders</i>	Common	headache
	Uncommon	paraesthesia
	Rare	convulsions (see section 4.4)
<i>Gastrointestinal disorders</i>	Common	diarrhea, vomiting, nausea, abdominal pain
	Uncommon	antibiotic-associated colitis (see section 4.4)
<i>Hepatobiliary disorders</i>	Common	transaminases increased, blood alkaline phosphatase increased, blood lactate dehydrogenase increased.
	Uncommon	blood bilirubin increased
<i>Skin and subcutaneous tissue disorders</i>	Common	rash, pruritus
	Uncommon	urticaria
	Not known	drug reaction with eosinophilia and systemic symptoms (DRESS syndrome), toxic epidermal necrolysis, Stevens Johnson syndrome, erythema multiforme

<i>Renal and urinary disorders</i>	Uncommon	blood creatinine increased, blood urea increased
<i>General disorders and administration site conditions</i>	Common	inflammation, pain
	Uncommon	Thrombophlebitis, pain at the injection site

Pediatric population

Meropenem is licensed for children over 3 months of age. There is no evidence of an increased risk of any adverse drug reaction in children based on the limited available data. All reports received were consistent with events observed in the adult population.

Reporting of suspected adverse reactions. Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

To report any side effect(s):

<ul style="list-style-type: none"> • _____: <p>- _____</p> <p>Fax: _____</p> <p>Call ____ at _____, Exts: _____.</p> <p>Toll free phone: _____</p> <p>E-mail ____@_____</p> <p>Website: _____</p>
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4.9. Overdose

Relative overdose may be possible in patients with renal impairment if the dose is not adjusted as described in section 4.2. Limited post-marketing experience indicates that if adverse reactions occur following overdose, they are consistent with the adverse reaction profile described in section 4.8, are generally mild in severity and resolve on withdrawal or dose reduction. Symptomatic treatments should be considered.

In individuals with normal renal function, rapid renal elimination will occur.

Hemodialysis will remove meropenem and its metabolite.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: antibacterials for systemic use, carbapenems.

ATC code: J01DH02

Mechanism of Action

Meropenem exerts its bactericidal activity by inhibiting bacterial cell wall synthesis in Gram-positive and Gram-negative bacteria through binding to penicillin-binding proteins (PBPs).

Mechanism of Resistance

Bacterial resistance to meropenem may result from: (1) decreased permeability of the outer membrane of Gram-negative bacteria (due to diminished production of porins) (2) reduced affinity of the target PBPs (3) increased expression of efflux pump components, and (4) production of beta-lactamases that can hydrolyse carbapenems.

There is no target-based cross-resistance between meropenem and agents of the quinolone, aminoglycoside, macrolide and tetracycline classes. However, bacteria may exhibit resistance to more than one class of antibacterial agents when the mechanism involved include impermeability and/or an efflux pump(s).

Breakpoints

European Committee on Antimicrobial Susceptibility Testing (EUCAST) clinical breakpoints for MIC testing are presented below.

EUCAST clinical MIC breakpoints for meropenem (2013-02-11, v 3.1)

Organism	Susceptible (S) (mg/l)	Resistant (R) (mg/l)
<i>Enterobacteriaceae</i>	≤ 2	> 8
<i>Pseudomonas</i> spp.	≤ 2	> 8
<i>Acinetobacter</i> spp.	≤ 2	> 8
<i>Streptococcus</i> groups A, B, C and G	note 6	note 6
<i>Streptococcus pneumoniae</i> ¹	≤ 2	> 2
<i>Viridans</i> group <i>streptococci</i> ²	≤ 2	> 2
<i>Enterococcus</i> spp.	--	--
<i>Staphylococcus</i> spp.	note 3	note 3
<i>Haemophilus influenzae</i> ^{1, 2} and <i>Moraxella catarrhalis</i> ²	≤ 2	> 2
<i>Neisseria meningitidis</i> ^{2, 4}	≤ 0.25	> 0.25
Gram-positive anaerobes except <i>Clostridium difficile</i>	≤ 2	> 8
Gram-negative anaerobes	≤ 2	> 8
<i>Listeria monocytogenes</i>	≤ 0.25	> 0.25
Non-species related breakpoints ⁵	≤ 2	> 8

¹ Meropenem breakpoints for *Streptococcus pneumoniae* and *Haemophilus influenzae* in meningitis are 0.25 mg/l (Susceptible) and 1 mg/l (Resistant).

² Isolates with MIC values above the susceptible breakpoint are very rare or not yet reported. The identification and antimicrobial susceptibility tests on any such isolate must be repeated and if the result is confirmed the isolate sent to a reference laboratory. Until there is evidence

regarding clinical response for confirmed isolates with MIC values above the current resistant breakpoint they should be reported resistant.

³ Susceptibility of staphylococci to carbapenems is inferred from the cefoxitin susceptibility.

⁴ Breakpoints relate to meningitis only.

⁵ Non-species related breakpoints have been determined using PK/PD data and are independent of MIC distributions of specific species. They are for use only for organisms that do not have specific breakpoints. Non species related breakpoints are based on the following dosages: EUCAST breakpoints apply to meropenem 1000 mg x 3 daily administered intravenously over 30 minutes as the lowest dose. 2 g x 3 daily was taken into consideration for severe infections and in setting the I/R breakpoint.

⁶ The beta-lactam susceptibility of streptococcus groups A, B, C and G is inferred from the penicillin susceptibility.

-- - Susceptibility testing not recommended as the species is a poor target for therapy with the drug. Isolates may be reported as R without prior testing.

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Lists of Microorganisms

Commonly susceptible species

Gram-positive aerobes:

Enterococcus faecalis[§]

Staphylococcus aureus (methicillin-susceptible)[‡]

Staphylococcus species (methicillin-susceptible) including *Staphylococcus epidermidis*

Streptococcus agalactiae (Group B)

Streptococcus milleri group (*S. anginosus*, *S. constellatus*, and *S. intermedius*)

Streptococcus pneumoniae, *Streptococcus pyogenes* (Group A).

Gram-negative aerobes:

Citrobacter freundii

Citrobacter koseri

Enterobacter aerogenes

Enterobacter cloacae

Escherichia coli

Haemophilus influenzae

Klebsiella oxytoca

Klebsiella pneumoniae

Morganella morganii

Neisseria meningitidis

Proteus mirabilis

Proteus vulgaris

Serratia marcescens.

Gram-positive anaerobes:

Clostridium perfringens

Peptoniphilus asaccharolyticus

Peptostreptococcus species (including *P. micros*, *P. anaerobius*, *P. magnus*)

Gram-negative anaerobes:

Bacteroides caccae

Bacteroides fragilis group

Prevotella bivia

Prevotella disiens.

Species for which acquired resistance may be a problem

Gram-positive aerobes

Enterococcus faecium[§].

Gram-negative aerobes

Acinetobacter species

Burkholderia cepacia

Pseudomonas aeruginosa.

Inherently resistant organisms

Gram-negative aerobes

Stenotrophomonas maltophilia

Legionella species.

Other micro-organisms

Chlamydomphila pneumoniae

Chlamydomphila psittaci

Coxiella burnetii

Mycoplasma pneumoniae

[§] Species that show natural intermediate susceptibility

‡ All methicillin-resistant staphylococci are resistant to meropenem

Glanders and melioidosis: Use of meropenem in humans is based on *in vitro* *B.mallei* and *B. pseudomallei* susceptibility data and on limited human data. Treating physicians should refer to national and/or international consensus documents regarding the treatment of glanders and melioidosis.

PK/PD relationship

Similar to other beta-lactam antibacterial agents, the time that meropenem concentrations exceed the MIC (T>MIC) has been shown to best correlate with efficacy. In preclinical models meropenem demonstrated activity when plasma concentrations exceeded the MIC of the infecting organisms for approximately 40 % of the dosing interval. This target has not been established clinically.

5.2 Pharmacokinetic properties

In healthy subjects the mean plasma half-life is approximately 1 hour; the mean volume of distribution is approximately 0.25 l/kg (11-27 l) and the mean clearance is 287 ml/min at 250 mg falling to 205 ml/min at 2 g. Doses of 500, 1000 and 2000 mg doses infused over 30 minutes give mean C_{max} values of approximately 23, 49 and 115 µg/ml respectively, corresponding AUC values were 39.3, 62.3 and 153 µg.h/ml. After infusion over 5 minutes C_{max} values are 52 and 112 µg/ml after 500 and 1000 mg doses respectively. When multiple doses are administered 8-hourly to subjects with normal renal function, accumulation of meropenem does not occur.

A study of 12 patients administered meropenem 1000 mg 8 hourly post-surgically for intra-abdominal infections showed a comparable C_{max} and half-life to normal subjects but a greater volume of distribution 27 l.

Pharmacokinetic studies performed in patients have not shown significant pharmacokinetic differences versus healthy subjects with equivalent renal function. A population model developed from data in 79 patients with intra-abdominal infection or pneumonia, showed a dependence of the central volume on weight and the clearance on creatinine clearance and age.

Distribution. The average plasma protein binding of meropenem was approximately 2 % and was independent of concentration. After rapid administration (5 minutes or less) the pharmacokinetics are biexponential but this is much less evident after 30 minutes infusion. Meropenem has been shown to penetrate well into several body fluids and tissues: including

lung, bronchial secretions, bile, cerebrospinal fluid, gynecological tissues, skin, fascia, muscle, and peritoneal exudates.

Biotransformation. Meropenem is metabolised by hydrolysis of the beta-lactam ring generating a microbiologically inactive metabolite. In vitro meropenem shows reduced susceptibility to hydrolysis by human dehydropeptidase-I (DHP-I) compared to imipenem and there is no requirement to co-administer a DHP-I inhibitor.

Elimination. Meropenem is primarily excreted unchanged by the kidneys; approximately 70 % (50 –75 %) of the dose is excreted unchanged within 12 hours. A further 28% is recovered as the microbiologically inactive metabolite. Faecal elimination represents only approximately 2% of the dose. The measured renal clearance and the effect of probenecid show that meropenem undergoes both filtration and tubular secretion.

Pharmacokinetics in Special Populations

Renal insufficiency. Renal impairment results in higher plasma AUC and longer half-life for meropenem. There were AUC increases of 2.4 fold in patients with moderate impairment (CrCL 33-74 ml/min), 5 fold in severe impairment (CrCL 4-23 ml/min) and 10 fold in hemodialysis patients (CrCL <2 ml/min) when compared to healthy subjects (CrCL >80 ml/min). The AUC of the microbiologically inactive ring opened metabolite was also considerably increased in patients with renal impairment. Dose adjustment is recommended for patients with moderate and severe renal impairment (see section 4.2).

Meropenem is cleared by hemodialysis with clearance during hemodialysis being approximately 4 times higher than in anuric patients.

Hepatic insufficiency. A study in patients with alcoholic cirrhosis shows no effect of liver disease on the pharmacokinetics of meropenem after repeated doses.

Pediatrics. The pharmacokinetics in infants and children with infection at doses of 10, 20 and 40 mg/kg showed C_{max} values approximating to those in adults following 500, 1000 and 2000 mg doses, respectively. Comparison showed consistent pharmacokinetics between the doses and half-lives similar to those observed in adults in all but the youngest subjects (<6 months half-life is 1,6 hours). The mean meropenem clearance values were 5.8 ml/min/kg (6-12 years), 6.2 ml/min/kg (2-5 years), 5,3 ml/min/kg (6-23 months) and 4.3 ml/min/kg (2-5 months). Approximately 60 % of the dose is excreted in urine over 12 hours as meropenem with a further 12 % as metabolite. Meropenem concentrations in the CSF of children with meningitis are approximately 20 % of concurrent plasma levels although there is significant inter-individual variability.

The pharmacokinetics of meropenem in neonates requiring anti-infective treatment showed greater clearance in neonates with higher chronological or gestational age with an overall average half-life of 2.9 hours. Monte Carlo simulation based on a population PK model showed that a dose regimen of 20 mg/kg 8 hourly achieved 60 % T>MIC for *P. aeruginosa* in 95 % of pre-term and 91 % of full term neonates.

Elderly. Pharmacokinetic studies in healthy elderly subjects (65-80 years) have shown a reduction in plasma clearance, which correlated with age-associated reduction in creatinine clearance, and a smaller reduction in non-renal clearance. No dose adjustment is required in elderly patients, except in cases of moderate to severe renal impairment (see section 4.2).

5.3. Preclinical safety data

Animal studies indicate that meropenem is well tolerated by the kidney. Histological evidence of renal tubular damage was seen in mice and dogs only at doses of 2000 mg/kg and above after a single administration and above and in monkeys at 500 mg/kg in a 7-day study.

Meropenem is generally well tolerated by the central nervous system. Effects were seen in acute toxicity studies in rodent at doses exceeding 1000 mg/kg.

The IV LD₅₀ of meropenem in rodents is greater than 2000 mg/kg.

In repeat dose studies of up to 6 months duration only minor effects were seen including a decrease in red cell parameters in dogs.

There was no evidence of mutagenic potential in a conventional test battery and no evidence of reproductive toxicity including teratogenic potential in studies in rats up to 750 mg/kg and in monkeys up to 360 mg/kg.

There was no evidence of increased sensitivity to meropenem in juveniles compared to adult animals. The intravenous formulation was well tolerated in animal studies.

The sole metabolite of meropenem had a similar profile of toxicity in animal studies.

5. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Meropenem 500 mg: anhydrous sodium carbonate

Meropenem 1 g: anhydrous sodium carbonate

6.2. Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3. Shelf life

Unopened vials: 3 years.

After reconstitution:

Intravenous bolus injection administration

A solution for bolus injection is prepared by dissolving the drug product in water for injection to a final concentration of 50 mg/ml. Chemical and physical in-use stability for a prepared solution for bolus injection has been demonstrated for 3 hours at up to 25°C or 16 hours under refrigerated conditions (2-8°C).

From a microbiological point of view the product should be used immediately.

If not used immediately in-use storage times and conditions are the responsibility of the user.

Intravenous infusion administration

A solution for infusion is prepared by dissolving the drug product in either 0.9% sodium chloride solution for infusion or 5% dextrose solution for infusion to a final concentration of 1 to 20 mg/ml. Chemical and physical in-use stability for a prepared solution for infusion using 0.9% sodium chloride solution has been demonstrated for 3 hours at up to 25°C or 24 hours under refrigerated conditions (2-8°C). Reconstituted solution of the product in 5% dextrose solution should be used immediately. The constituted solutions should not be frozen.

6.4. Special precautions for storage

Do not store above 30°C.

For storage conditions of the reconstituted medicinal product, see section 6.3. Do not freeze the reconstituted solution.

6.5 Nature and contents of container

Meropenem 500 mg powder for solution for IV Injection or Infusion

674 mg powder in 10 ml glass vial with rubber stopper and aluminium or flip-off cap.

Meropenem 1 g powder for solution for IV Injection or Infusion

1348 mg powder in 20 ml glass vial with rubber stopper and aluminium or flip-off cap.

The vials are packed in boxes of 1, 5, 10, 1-50 or 50 vials.

Not all pack sizes may be marketed.

6.6. Special precautions for disposal and other handling

The use of freshly prepared solutions is recommended. For storage conditions of the reconstituted medicinal product, see section 6.3.

Intravenous bolus injection administration

A solution for bolus injection is prepared by dissolving the drug product in water for injection to a final concentration of 50 mg/ml (see table below).

Vial size	Amount of diluent (ml)	Approximate withdrawable volume (ml)	Approximate average concentration (mg/ml)
500 mg	10	10	50
1 g	20	20	50

Standard aseptic techniques should be used for solution preparation and administration. The solution should be shaken before use.

Intravenous infusion administration

A solution for infusion is prepared by dissolving the drug product in either 0.9% sodium chloride solution for infusion or 5% dextrose solution for infusion to a final concentration of 1 to 20 mg/ml. Standard aseptic techniques should be used for solution preparation and administration.

The solution should be shaken before use.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. Marketing authorisation holder

“KRASPHARMA” OJSC

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Tel.: +7 (391) 261-25-90. Fax: +7 (391) 261-17-44

8. Marketing authorisation number(s)

Meropenem 500 mg Powder for Solution for IV Injection or Infusion _____

Meropenem 1 g Powder for Solution for IV Injection or Infusion _____

9. Date of first Authorisation / renewal of the authorisation

10. Date of revision of the text

_____.